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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,661	KULOWSKI ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed February 2, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-9 and 17-19 were pending (Applicants canceled claims 10-16 in Paper No. 4). Applicants presently canceled claims claim 1 and amended claims 2, 3, 4-6, and 17. Therefore, claims 2-9 and 17-19 are pending and examined on the merits.

Withdrawn Objections/Rejections

4. The objection to claims 1 and 4 are withdrawn in view of Applicants' amendments thereto and/or cancellation of claims. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted B and D are withdrawn in view of Applicants' amendments to the claims and/or cancellation of claims. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 2-9 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 2-9 and 17-19 are drawn to a genus of methods for producing "biocatalysts" using "host cells" that contain at least two "biotransformation genes" that are capable of producing "biocatalysts" that can modify "substrates" inside the host cells. The scope of these claims include an infinite number of methods for producing an infinite number of recombinant host cells (i.e., host cells with an infinite number of different "biotransformation genes") that will generate an infinite number of "biocatalysts" that will react with an infinite number of "substrates" to produce an infinite number of products wherein no distinguishing structural attributes are provided for the members of either the biotransformation genes, biocatalysts, substrates or products. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the biotransformation genes, biocatalysts, substrates or products.

Although the specification provides one "hypothetical" example of a monoterpene substrate reacted with host cells that contain p450/o-methyltransferase plasmid constructs and also a "laundry list" of other "potential" substrates and enzymes (e.g., see specification, pages 10-11), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these biotransformation genes, biocatalysts, substrates and products. Consequently, it is not possible to determine *a priori* which compounds

the would be encompassed by Applicants' broad claims because there is no common structural attributes that can link together ***all*** of these potential biotransformation genes, biocatalysts, substrates and products i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of compounds that should be included in this broad genus from the ONE "working" example provide by applicant (i.e., the use of p450/o-methyltransferase with a monoterpene) (the word "working" is placed in quotations because Applicants do not actually characterize any of the products here, it is a complexly "hypothetical" example and thus NOT a true working example).

Thus, the specification provides only ONE "hypothetical" example (see specification, page 10, lines 27-28; see also page 11) for the biocatalysis of a monoterpene. One representative species (i.e., biocatalysis of a monoterpene) is not enough to show possession of a genus that would encompass an infinite number of possibilities i.e., ***any*** substrate using ***any*** enzyme to form ***any*** product.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above

(for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Although several other biometabolic pathways are known in the art in addition to the "hypothetical" monoterpene biosynthesis example provided by applicant (see 35 USC 102 rejections below), a written description of all biometabolic pathways is still not possible. In order to achieve possession of these broad claims, all genes associated with every biometabolic enzyme would have to be known (i.e., characterized), expressable (i.e., cloned) and be able to be functionally expressed (i.e., active in new host), which is simply not the case. \

For example, even within the limited scope of the carotenoid biosynthetic pathway (which would be encompassed by Applicants' broad claims) all genes encoding all biometabolic enzymes have not been achieved. For example, applicants cannot express zeaxanthin epoxidase from *Nicotiana* in *E.coli* because this prokaryotic host cannot provide reduced ferredoxin, which is needed for epoxide formation i.e., to be functionally expressed (see Sandmann G.; Albrecht, M.; Schnurr, G.; Knorzer, O.; Boger, P., "The biotechnological potential and design of novel carotenoids by gene combination in *Escherichia coli*" Trends. Biotechnol. **1999**, 17, 233-237, see especially 234, column 2, paragraph 1).

Furthermore, the possibility of expressing new enzymes (which would also be encompassed by Applicants' broad claims) is either hit or miss since it does not depend on any rational basis for experimentation i.e., molecular modeling, etc. Furthermore, this "hit or miss" technology may be subject to poor screening techniques for a desired

mutant (see Schmidt-Danert, C.; Arnold, F. H. "Directed evolution of industrial enzymes" The International Business Communications Second International Symposium on Directed Evolution of Industrial Enzymes, September 1998, see section on "Screening technology") ("There was consensus among the participants that one critical phase of any directed-evolution experiment is deciding how to search for variants with the desired properties. For most practical problems, this search is both time consuming and expensive").

Therefore, applicants are not is possession of ***any*** host cell comprising ***any*** biotransformation genes that encode ***any*** biocatalyst for the production of ***any*** product. Applicants' claimed scope represents only an invitation to experiment regarding possible biometabolic enzymes that might be clones and used for a given metabolic pathway.

Furthermore, Applicants employ only "functional language" to describe critical elements of their invention. With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. Here, Applicant's describe the "biocatalysts" only by what they can do i.e., catalyze an unspecified reaction. The CAFC

held this sort of functional definition insufficient to adequately describe the claimed product.

Given this lack of description of the representative species encompassed by the genus of the claims and the "improper" use of functional language, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-9 and 17-19.

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that they do not have to define the term "biocatalyst" because it is clear based on the numerous citations in the prior art e.g., U.S. Patent 6,638,758, 6,642,020, 6,638,419 ... etc. (e.g., see 2/2/2004 Response, page 13, last paragraph).

[2] Applicants argue that their description of the term "biocatalyst" is "far more substantive than most of the patents" (e.g., see 2/2/2004 Response, page 13, last paragraph).

[3] Applicants argue that the Examiner has not set forth any reasons "why the specification does not provide a disclosure commensurate in scope with the requirements of 35 USC 112, first paragraph" and that a written description rejection based solely on the enormous

"breadth of the claims" is "per se invalid" as shown by *In re Robins, Ex parte Laiderman, In re Edwards, Rice and Soulen* (e.g., see 2/2/2004 Response, pages 14-15).

This is not found persuasive for the following reasons:

[1] The Examiner contends that each U.S. Patent is examined on its own merits and in light of the submitted specification and, as a result, applicants' arguments are moot. For example, the following U.S. Patents each set forth completely different definitions for the term "biocatalyst" which clearly demonstrates that the prior art does not provide a consistent definition for the term. Thus, Applicants statement that the term biocatalyst has "a well understood meaning in the art" is clearly false. Please note that there are many more examples (too numerous to list) and that these references are only set forth for the sole purpose of refuting Applicants' arguments (see also 35 U.S.C. 112, second paragraph rejection below).

(a) U.S. Patent No. 4,092,245 defines the term "biocatalyst" as "a microbicide or microbicidal catalyst composition in the form of a finely divided substance capable of being used in a filter medium through which the liquid to be treated is passed so that contact with the microbicide will destroy microorganisms" and provide aqueous mixture of "lampblack, silver oxide, and zinc oxide" as an example (e.g., see column 1, lines 36-42).

(b) U.S. Patent No. 5,567,451 defines the term "biocatalyst" as "a system which is capable of effecting a biochemical reaction, starting from a substrate, under appropriate conditions" and provide calcium aliginate beads as an example (e.g., see column 2, lines 7-10; see also Examples).

(c) U.S. Patent No. 5,486,292 defines the term "biocatalyst" as "a variety of chemically active living microorganisms, such as bacteria, yeast" (e.g., see column 1, lines 44-46). Please note that this definition does not include enzymes or cell lysates and thus explicitly contradicts U.S. Patent No.

(d) U.S. Patent No. 5,910,440 defines the term "biocatalyst" as "any organism or fraction of an organism (e.g., cell fraction, cell extract, crude or purified enzyme preparation) capable of performing the desired reaction" (e.g., see column 1, lines 51-44). Please note that this definition is not limited to "microorganisms" and thus contradicts U.S. Patent 5,486,292 ('292). It also includes enzymes and cell extracts which '292 does not include.

Furthermore, Applicants' specification explicitly states that they are not relying on the "well understood meaning in the art" and, as a result, Applicants 2/2/2004 Response contradicts their own specification (e.g., compare 2/2/2004 Response, page 13, paragraph bridging pages 13-14 wherein Applicants state that the term would be clear from the well understood meaning in the art to the specification at page 4, paragraph 1 wherein Applicants state, "The biocatalyst may remain intact through the intended biochemical reaction or may react with starting compounds containing this functional group. Although this is not within the classic definition [i.e., does not fall within the "well understood" meaning] of catalysts, it is within the scope of the present invention").

[2] The Examiner respectfully disagrees. While Applicants provide "examples" of biocatalysts, they do not provide a "definition" for the term like the patents cited above (e.g., see page 10 of the specification, lines 6-7 "Examples of biocatalysts of the invention include but are

not limited to monooxygenases; dioxygenases; methyltransferases; and glycosyltransferases"). Furthermore, Applicants' specification would render any prior art definition unclear because Applicants explicitly denounce those definitions (e.g., see specification, page 4, paragraph 1, "The biocatalyst may remain intact through the intended biochemical reaction or may react with starting compounds containing this functional group. Although this is not within the classic definition (i.e., their definition does NOT fall within any "well accepted" meaning) of catalysts, it is within the scope of the present invention").

[3] Finally, the Examiner respectfully contends that Applicants are factually mistaken. The original rejection has set forth at length many reasons why Applicants' specification does not provide a disclosure commensurate in scope with the requirements of 35 USC 112, first paragraph (see bolded and underlined portions of the original rejection below).

> Although several other biometabolic pathways are known in the art in addition to the "hypothetical" monoterpene biosynthesis example provided by applicant (see 35 USC 102 rejections below), a written description of all biometabolic pathways is still not possible. **In order to achieve possession of these broad claims, all genes associated with every biometabolic enzyme would have to be known (i.e., characterized) [i.e., reason #1], expressable (i.e., cloned) [i.e., reasons #2] and be able to be functionally expressed (i.e., active in new host) [i.e. reason #3], which is simply not the case.**
>
> For example, even within the limited scope of the carotenoid biosynthetic pathway (which would be encompassed by Applicants' broad claims) all genes encoding all biometabolic enzymes have not been achieved. For example, applicants cannot express zeaxanthin epoxidase from *Nicotiana* in *E.coli* because this prokaryotic host cannot provide reduced ferredoxin, which is needed for epoxide formation i.e., to be functionally expressed (see Sandmann G.; Albrecht, M.; Schnurr, G.; Knorzer, O.; Boger, P., "The biotechnological potential and design of novel carotenoids by gene combination in *Escherichia coli*" Trends. Biotechnol. **1999**, 17, 233-237, see especially 234, column 2, paragraph 1) **[i.e., the Examiner is providing a specific "literature" example for reasons #3 which was NOT refuted by Applicants]**.
>
> Furthermore, the possibility of expressing new enzymes (which would also be encompassed by Applicants' broad claims) **is either hit or miss since it does not depend on any rational basis for experimentation i.e., molecular modeling, etc [i.e., reason #4]**. Furthermore, this "hit or miss" technology may be subject to poor screening techniques for a desired mutant (see Schmidt-Danert, C.; Arnold, F. H. "Directed evolution of industrial enzymes" The International Business Communications Second International Symposium on Directed Evolution of Industrial Enzymes, September 1998, see section on "Screening technology") ("There was consensus among the participants that one critical phase of any directed-evolution experiment is deciding how to search for variants with the desired properties. For most practical problems, this search is both time consuming and expensive") **[i.e., the Examiner is providing a specific "literature" example of reason #4 which was NOT refuted by Applicants]**.

Clearly, at least four reasons including specific literature examples have been set forth by the Examiner, which Applicants have not refuted in any way. Thus, Applicants cited case law (drawn to rejections based solely on breadth) is simply not on point. In addition, the Examiner notes that Applicants have failed to address any of the more recent CAFC decisions with regard to written description i.e., cases decided within the last 30 years (Applicants only cite CCPA decisions from the early 1970s), which were set forth by the Examiner (e.g., Lilly which was decided in 1997) and appear to be more on point. Finally, the Examiner contends that even if *assuming arguendo* that (1) Applicants' cited cases were controlling here and (2) no reasons were set forth by the Examiner why Applicants should not be entitled to this enormous scope (which is clearly not the case), these old cases do not establish a "per se rule" against written description rejections based solely on the enormous and seemingly unbounded breadth of Applicants' claims.

Finally, the Examiner notes that Applicants have not addressed the Examiner's "functional language" argument and thus the Examiner contends that Applicants have conceded this point (e.g., see last two paragraphs of original rejection).

Accordingly, the written description rejection cited above is hereby maintained.

7. Claims 1-9 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a library of hosts cells containing plasmids encoding cytP450I, OMT and cytP450II (see specification, page 12, Table 1), does not reasonably provide enablement for ***any*** host cell containing a library of ***any*** biotransformation genes encoding ***any*** set of biocatalysts to produce ***any*** products. The specification does not enable any person skilled

in the art to which it pertains, or with which it most nearly connected, to make and use the invention commensurate in scope with these claims. This is an enablement rejection.

Despite knowledge in the art for pathways other than the biocatalytic conversion of a monoterpene (see 35 USC 102 rejections below), the specification fails to provide guidance regarding how to create a library of host cells with genes that encode for ***any*** biocatalyst associated with ***any*** biometabolic pathway. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to a broad genus. The scope of these claims include an infinite number of methods for producing an infinite number of recombinant host cells (i.e., host cells with an infinite number of different "biotransformation genes") that will generate an infinite number of "biocatalysts" that will react with an infinite number of "substrates" to produce an

infinite number of products wherein no distinguishing structural attributes are provided for the members of either the biotransformation genes, biocatalysts, substrates or products. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the biotransformation genes, biocatalysts, substrates or products. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Combinatorial biosynthesis is a new and highly unpredictable field that requires identification/characterization of the "modular biosynthetic enzymatic machinery." With the exception of polyketides and nonribosomally produced peptides and carbohydrates, this has not been done. For example, Taylor states that for the biosynthesis of epothione would require a mixed NRPS/PKS "biosynthetic enzymatic machinery." However, Taylor states that there are currently "no examples of such an approach [in the literature]" and that while it may be "easy to imagine how novel epothione analogs could be generated" (much like Applicants' "hypothetical" example for making monoterpene derivatives), "[m]uch work remains to be done in elucidating the organization and structure of hybrid PKSs/NRPSs, however, before combinatorial biosynthesis with these systems can be undertaken" (emphasis added) (see Taylor, S. V. in "Handbook of Combinatorial Chemistry" Eds. Nicolaou, K. C.; Hanko, R.; Hartwig, W. Weinheim Germany: Wiley-VCH 2002, Vol. 2, page 1075, last paragraph).

Another example is the carotenoid biosynthetic pathway (which would be encompassed by Applicants' broad claims) wherein the "biocatalyst" zeaxanthine epoxidase cannot be expressed in *E. coli.* because this prokaryotic host cannot provide reduced ferredoxin, which is needed for epoxide formation i.e., to be functionally expressed (see Sandmann G.; Albrecht, M.; Schnurr, G.; Knorzer, O.; Boger, P., "The biotechnological potential and design of novel carotenoids by gene combination in *Escherichia coli*" *Trends. Biotechnol.* **1999**, 17, 233-237, see especially 234, column 2, paragraph 1).

Therefore, the Examiner contends that the level of predictability in the art is low.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided a single working example etc. Applicants present only one "hypothetical" example for the biosynthesis of monoterpene derivatives.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working

examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response

8. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "The entire underpinning of the rejection set forth in the Office Action is an attack on the breadth of the claims, the sparse number of the examples, and other factors that are not material to the underlying nature of the requirements of the statute as defined by case law" and cite *In re Marzocchi and Horton* in support of their position i.e., Applicants contend that *In re Marzocchi*, a 1970s CCPA decision, somehow invalidates the later decided *In re Wands*, a 1988 CAFC decision (e.g., see 2/2/2004 Response, pages 15-16, "the breadth of the claims [i.e., Wand Factor #1], the sparse number of examples [i.e., Wand factors #6-7] and other factors [i.e., presumably the rest of the Wands factors] are not material ... as defined by case law") (emphasis added).

This is not found persuasive for the following reasons:

The Examiner respectfully contends that Applicants are legally and factually mistaken. First, the Examiner notes that the proper legal standard for Enablement (i.e., the factors to be considered) and the policy that has been adopted by the U.S. Patent and Trademark Office has been set forth in *In re Wands* (e.g., see *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); see also MPEP § 2164.01 where the "*In re Wands* test" for Enablement is disclosed; see especially MPEP § 2164.01(a) wherein the "eight" factors are disclosed in detail). Thus, Applicants would appear to be applying the wrong legal standard.

Second, the Examiner notes that the original rejection is not based solely on breadth "as the entire underpinning of the rejection" i.e., this is a factually mistake. The rejection is based on the "eight" *In re Wand* factors as set forth in the original rejection wherein "breadth" is but one factor (i.e., Wand factor #1). Furthermore, the Examiner notes that Applicants have not addressed and/or refuted any of "*In re Wands* factors" and, as a result, Applicants concede these points.

Accordingly, the Enablement rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 112

9. Claims 2-9 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claims 2,17*** are rejected because the "biocatalysts" in these claims is not defined with any chemical or physical characteristic, but only by functional properties i.e., their ability to catalyze a biochemical reaction. A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide/protein with this function i.e., biocatalytic activity. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Therefore, claims 2,17 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

B. Withdrawn.

C. For **claim 2**, the phrase "introduce two different chemical functional groups, at least one of the at least two different chemical functional groups for catalyzing processes for selected from the group selected from forming carbon to carbon bonds, hydroxylation ... " is vague and indefinite. For example, "hydroxylation" is NOT a "chemical functional group" i.e., a "hydroxyl" group is a functional group, hydroxylation is a process by which a "hydroxyl group" is introduced. Applicants are requested to clarify and/or correct. Therefore, claims 2 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. Withdrawn.

E. ***Claims 5-8*** are rejected because the "biotransformation genes" in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., their ability to provide "functional group addition of groups capable of providing

catalysis for processes selected from the group consisting of acylation ... etc." A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide/protein with this function i.e., biocatalytic activity. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169.

Furthermore, it is not clear what Applicants' are referring to here. Do the biotransformation genes encode proteins that catalyze the addition of functional groups that "can be" acted on by enzymes that catalyze reactions for acylation, glycosylation, amidation? Do the biotransformation genes encode the "acylation, glycosylation, amidation" enzymes themselves? Do the genes act as substrates that are subsequently transformed into said functional group? Applicants intent here is simply not clear. Therefore, claims 5-8 and all dependent claims are rejected under 35 USC 112, second paragraph.

Response

10. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

A. **[1]** Applicants argue, "the term biocatalyst is found in 627 separate US Patents as of 17 November 2003 ... [thus] the term has an established and clear meaning" (e.g., see 2/2/2004 Response, page 16, second to last paragraph).

[2] Applicants argue, "beyond the clear definition in the specification that is consistent with standard usage in the art, is not needed" and cite Ex parte Olson in defense of this position (e.g., see 2/2/2204 Response, page 16, second to last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that each Patent is examined on its own merits and, as a result, Applicants' arguments are moot. However, even if assuming arguendo that the 627 US Patents were relevant to the issue at hand, the Examiner contends that the definitions provided by the 627 patents are not consistent with any one definition and thus she no light on the meaning of the term (e.g., see 35 U.S.C. 112, first paragraph rejection response with regard to Written Description, which addressed this issue at length and is incorporated in its entirety herein by reference i.e., compare the conflicting definitions for US Patents Nos. (a) 5,567,451, (b) 5,567,451, (c) 5,486,292, (d) 5,910,440. Furthermore, even if assuming arguendo that the prior art does provide a "clear" definition for the term, the Examiner contends that Applicants have not addressed the "functional language" part of the rejection under *ex parte Pulvari* and thus have conceded this point.

[2] The Examiner contends that the term is not "clear" from the specification and thus Ex parte Olson does not apply. Furthermore, Applicants have not state what patents (i.e., which out of the 627) they wish to be "consistent" with because clearly not all 627

patents provide the same definition (e.g., see response [1] above; see also 35 U.S.C. § 112, first paragraph rejection response to Written Description, which is incorporated in its entirety herein by reference).

C. Applicants argue that they have placed the group in "a parallel Markush Group" format and thus have overcome the rejection (e.g., see 2/2/2004 Response, page 17, lines 3-4) without providing any rationale for why this "parallel" format overcomes the rejection.

This is not found persuasive for the following reasons:

The Examiner contends that the "parallel Markush Group" format only makes it worse (e.g., see new 35 U.S.C. 112, second paragraph rejection below) and, as a result, the claim is still indefinite for the reasons of record i.e., hydroxylation and halogenation still don't represent "functional groups" (emphasis added).

E. Applicants argue, "contrary to the assertions of the Examiner, the predictability of the synthesis is quite high" and then provides a rationale for why "attaching groups of specific functionality to a cell would be readily [achievable]" (e.g., see 2/2/2004 Response, pages 17-18).

This is not found persuasive for the following reasons:

The Examiner contends that Applicants' assertion that the predictability of synthesis in the art is quite high is wholly unsubstantiated (i.e., no evidence has been presented) and is not relevant to the rejection. Furthermore, Applicants arguments with respect to the "attachment" are also not relevant. The Examiner is arguing that a person of skill in the art cannot "immediately" envision *a priori* all the different proteins that

would be useful in "biotransformation" and certainly could not envision all the different genes that encode said proteins. Furthermore, Applicants have failed to address the point of reference argument set out in the second paragraph of the original rejection.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

Claims Rejections - 35 U.S.C. 102

11. Claims 2-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Xue et al. (Xue, Q.; Ashley, G.; Hutchinson, C. R.; Santi, D. V. "A multiplasmid approach to preparing large libraries of polketides" PNAS, **October 12, 1999**, 96(21), 11740-11745).

For ***claim 2***, Xue et al. disclose a collection (library) of recombinant *Streptomyces lividans* (i.e., host cell) carrying various combinations of three plasmids (i.e., recombining at least two biotransformation genes encoding proteins for modifying a chemical substrate) representing mutant and/or wild type including eryAI, eryAII and eryAIII genes encoding for modules 1-2, 3-4, and 5-6 of the DEBS 1, 2 and 3 modular proteins (biometabolic enzymes), respectively (see Xue et al., page 11741, figure 1, showing wild type and mutant forms of eryA genes and DEBS proteins; see also page 11743, table 1, showing genotype of plasmids containing DEBS genes that were combined to produce a library of host cells for the generation of new macrolactones i.e., see macrolactones in figure 3).

Xue et al. disclose modifying the substrate propionyl-CoA in the recombinant host cells (see Xue et al., page 11741, figure 1 see also page 11743, second column, last paragraph) ("In one example, we prepared a single Cys-729 → Ala mutation at the KS1 domain of DEBS1 module 1. The inactive KS1 prevents propagation of the starter unit and permits introduction of exogenous synthetic diketide thiol esters into position 12 and 13 of the 14-membered macrolide product. The plasmid encoding the KS1 null allele of eryAI was introduced by cotransformation into *S. lividans* with the 1 eryAII mutant and 7 eryAIII mutants (Table 1) to provide ***16 transformants*** [each containing more than one mutation])."

Xue et al. states, that "[b]y using this multiple plasmid approach, with X mutants of ORF 1, Y mutants of ORF 2 and Z mutants of ORF 3, along with the wild-type genes, for instance, a ***combinatorial library*** of (X+1) × (Y+1) × (Z+1) ***mutants*** plus the wild-type PKS could be created expeditiously" (see Xue et al., page 11740, bottom of last paragraph) (see also Xue et al., page 11742, second column, last paragraph, stating "[a] demonstration ***library*** composed of ***three single mutations*** in eryAI (module 2), one in eryAII (module 3), and seven in eryAIII (modules 5 or 6) as well as wild-type ORFs was created by using this three-plasmid system"). Xue et al. also mentions the use of DNA shuffling techniques to prepare larger libraries of polyketides (see Xue et al., page 11740, column 2 second to last paragraph, "[a]nother strategy for preparing large numbers of polyketides is by random digestion-religation leading to "mutagenesis" of the domains or modules of a mixture of PKS genes, including the refinements embodied in the DNA shuffling method").

Furthermore, each mutant is "operably controlled" under the direction of the actI promoter and actII-ORF4 gene (see Xue et al., page 11742, figure 2) for the production of modular enzymes (biometabolic) that are involved in the polyketide biosynthetic pathway and the enzymes in these constructs create new biometabolic pathways producing new macrolactone derivatives (i.e., the enzyme is isolated from a biometabolic pathway that is different from the biometabolic pathway of which it is a component in the host cell and the mutated gene is a chimera of genes from different metabolic pathways e.g., erythromycin and rapamycin biometabolic pathways). Therefore, Xue et al. anticipates all of the limitations in claim 1.

Finally, Xue et al. disclose the introduction of different chemical groups including a ketone and a carbon-carbon double bond. The carbon-carbon double bond reads on Applicants' claims because it discloses the formation of a "carbon to carbon bond" (see Xue et al., figure 1B). Furthermore, Xue et al. disclose two different "carbon to carbon bond" formations (e.g., see Figure 3, wherein structures 1-48 have different carbon-carbon bond formations and also different hydroxylation patterns).

For ***claims 3-4***, Xue et al. disclose many reactions including oxidation (e.g., see Xue et al., figure 1 B wherein a hydroxyl group is oxidized to a ketone).

For ***claim 5***, Xue et al. disclose compound 21 (see Xue et al., page 11744, figure 3), which has an almost identical in structure to Applicants' elected narbonolide species and thus would be expected to undergo "glycosylation" as shown by Applicants' "Diagrammatic Description of Species Example of Claim 19" (see Paper No. 4). Xue et al. also states that the "PKS libraries generated could be leveraged and expanded by

introducing genes for tailoring enzymes that oxidize, methylate, acylate, or glycosylate the product of the PKS" (see Xue et al., page 11745, column 1). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 6-9***, Xue et al. disclose Applicants' elected *Streptomyces lividans* host cells and both constitutive and inducible promoters to create whole cell biocatalysts (see Xue et al., page 11741-42, Materials and Methods; see also figure 2).

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "there is no specific teaching of these limitations of adding <u>different biocatalyst functions</u> onto the same substrate" (e.g., see 2/2/2004 Response, pages 18-19, especially page 19, first full paragraph).

[2] Applicants ague, "The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference" (e.g., see 2/2/2004 Resposne, page 19, paragraph 1).

[3] Applicants argue that the 35 U.S.C. 102 rejection "undercuts" the 35 U.S.C. 112, first paragraph rejection (e.g., see 2/2/2004 Response, page 19, paragraph 2).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully contends that Applicants' arguments are not clear. There are no "different biocatalyst functions" recited in the claims as purported by Applicants. There are "different chemical functional groups", but not "different biocatalysts functions" (e.g., see claim 2). Thus, Applicants arguments are not commensurate in scope with the claimed invention.

[2] These statements are wholly unsubstantiated and thus without merit. Furthermore, the original rejection sets forth in great detail every element of the claimed invention and, as a result, contradict these assertions.

[3] Applicants' argument is not convincing since the above 35 U.S.C. 112, first paragraph rejections are "scope" rejections, which indicates, that a "portion" of Applicants' invention is indeed enabled by the specification, but points out that a much larger portion of the claimed invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

13. Claims 2-3 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Stachelhaus et al. (Stachelhaus, T.; Schneider, A.; Marahiel, M. A. "Rational Design of Peptide Antibiotics by Targeted Replacement of Bacterial and Fungal Domains" Science, **July 1995**, 269, 69-72).

For ***claim 2***, Stachelhaus et al. disclose a collection (library) of *E. coli* and *B. subtilis* strains (i.e., host cells) carrying various chimeric peptide synthetase constructs (See Stachelhaus et al., page 72, table 1). Stachelhaus et al. disclose recombining "at least two" biotransformation genes including srfA gene from *B. subtilis* with the Phe, Orn, and Leu activating domains from the grs operon from *Bacillus brevis* (replacing the Leu srfA-C from *B. subtilis*) to form a gene chimera from different organisms i.e., recombining at least two biotransformation genes encoding proteins for modifying a chemical substrate (see Stachelhaus et al., page 73, table 1; see also page 70, column 1, paragraph 3; see also figure 4 showing replacement of "at least two" biotransformation genes into each of the [Cys^7]surfactin "isoforms"). Furthermore, these chimeric peptide synthetase constructs encode for synthetases (i.e., biocatalysts) that are used to produce peptides by a nonribosomal mechanism and the enzyme in these constructs creates new biometabolic pathways producing new peptide derivatives (i.e., the enzyme is isolated from a biometabolic pathway that is different from the biometabolic pathway of which it is a component in the host cell and the mutated gene is a chimera of genes from different

metabolic pathways), which anticipates claim 1 (see Stachelhaus et al., page 72, table 1; see also pages 70-71, figures 1-3).

Finally, Stachelhaus et al. disclose the addition of Cys, Phen, Orn, Leu and Val into the surfactin isoforms that would read on the introduction of "at least two different" carbon-carbon bonds (see page 72, Table 1).

For ***claim 3***, Stachelhaus et al. disclose replacement of leucine for Cys, Phe, Orn, Val (see page 72, Table 1).

For ***claim 5***, Stachelhaus et al. disclose acylation or glycosylation (see page 72, column 2, paragraph 1).

For ***claim 6-8***, Stachelhaus et al. disclose *E. coli* and *B. subtilis* (see Stachelhaus et al., page 72, table 1). Stachelhaus et al. also discloses an srfA-C integration vector under the control of a heat inducible tandem P_r/P_l promoter (see page 70, figure 2) that was used to create the library of recombinant host cells with the expression vectors.

Response

14. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate" (e.g., see 2/2/2004 Response, pages 19, last paragraph).

[2] Applicants ague, "The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference" (e.g., see 2/2/2004 Response, page 19, paragraph 1).

[3] Applicants argue that the 35 U.S.C. 102 rejection "undercuts" the 35 U.S.C. 112, first paragraph rejection (e.g., see 2/2/2004 Response, page 20, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully contends that Applicants' arguments are not clear. There are no "different biocatalyst functions" recited in the claims as purported by Applicants. There are "different chemical functional groups", but not "different biocatalysts functions" (e.g., see claim 2). Thus, Applicants arguments are not commensurate in scope with the claimed invention.

[2] These statements are wholly unsubstantiated and thus without merit. Furthermore, the original rejection sets forth in great detail every element of the claimed invention and, as a result, contradict these assertions.

[3] Applicants' argument is not convincing since the above 35 U.S.C. 112, first paragraph rejections are "scope" rejections, which indicates, that a "portion" of Applicants' invention is indeed enabled by the specification, but points out that a much larger portion of the claimed

invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

15. Claims 2-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Albrecht et al. (Albrecht, M.; Takaichi, S.; Misawa, N.; Schnurr, G.; Boger, P.; Sandmann, G. "Synthesis of atypical cyclic and acyclic hydroxy carotenoids in *Escherichia coli* transformants" *Journal of Biotechnology*, **1997**, 58, 177).

For ***claims 2-9***, Albrecht et al. disclose a collection (library) of *Escherichia coli* strains (i.e., recombinant host cells) carrying various plasmids (i.e., with at least two biotransformation genes encoding proteins for modifying a chemical substrate into the host cell) mutated to contain various carotenoic genes e.g., crtE, crtB, crtI, etc (see Albrecht et al., page 178, table 1) encoding enzymes (biocatalysts) for the production of various terpenoids (see Albrecht et al., page 182, figure 3). Albrecht et al. disclose *E. coli* host cells containing plasmids that have been mutated to carry more than one gene i.e., "at least two" (see Albrecht et al., page 178, table 1, e.g., pACCRT-EBI$_{Rc}$, pACCRT-EBI$_{Eu}$, etc). Furthermore, each vector mutated to express the terpenoid genes is "operably controlled" using different replicons (see Albrecht et al., page 178, table 1, which reads on claims 6-9) for the production of modular enzymes (biometabolic) that are involved in terpenoid biosynthesis (see Albrecht et al., abstract, "A total of eight

different hydroxyl carotenoids we reproduced in transformants of the non-carotenogenic bacterium Escherichia coli. They include the acyclic 1-hydroxyneurosporene, 1-hydroxylcopene, 1,1'-dihydroxylcopene, [etc]", which include the introduction of "at least two different chemical functional groups" and reads on claims 3-5), i.e., the mutated gene is a chimera of genes from different metabolic pathways (see for Albrecht et al., page 182, figure 3, for part (a) showing different metabolic pathways that produce different terpenoids via different chimeric enzymes) (see also Albrecht et al., abstract, for parts (b) and (c) showing carotenoids that are produced in "non-carotenogenic bacterium"). Therefore, Albrecht et al. anticipates all of the limitations in claims 2-9.

Response

16. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate" (e.g., see 2/2/2004 Response, pages 20, second to last paragraph).

[2] Applicants ague, "The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and

hypotheses, not upon actual teachings in the reference" (e.g., see 2/2/2004 Response, page 20, second to last paragraph).

[3] Applicants argue that the 35 U.S.C. 102 rejection "undercuts" the 35 U.S.C. 112, first paragraph rejection (e.g., see 2/2/2004 Response, page 20, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully contends that Applicants' arguments are not clear. There are no "different biocatalyst functions" recited in the claims as purported by Applicants. There are "different chemical functional groups", but not "different biocatalysts functions" (e.g., see claim 2). Thus, Applicants arguments are not commensurate in scope with the claimed invention.

[2] These statements are wholly unsubstantiated and thus without merit. Furthermore, the original rejection sets forth in great detail every element of the claimed invention and, as a result, contradict these assertions.

[3] Applicants' argument is not convincing since the above 35 U.S.C. 112, first paragraph rejections are "scope" rejections, which indicates, that a "portion" of Applicants' invention is indeed enabled by the specification, but points out that a much larger portion of the claimed invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

17. Claims 2-9 and 17-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Katz et al. (U.S. 2002/0111317 A1) (Date of Filing is **September 24, 2001**).

For ***claim 2-9 and 17-19***, Katz et al. (see entire document) disclose recombinant DNA compounds that encode the proteins required to produce sixteen-member macrolides as well as proteins that further modify these macrolides [including Applicants' elected narbomycin]. In one embodiment, recombinant DNA compounds that encode portions of these proteins are provided. In another aspect of the present invention, recombinant DNA compounds that encode a hybrid protein that is the product of one or more PKS genes are provided wherein the hybrid protein encodes all or portion of a protein involved in the biosynthesis of sixteen-membered macrolide. In one embodiment, the recombinant DNA compounds of the invention are recombinant DNA cloning vectors that facilitate manipulation of the coding sequences or recombinant DNA expression vectors that code for the expression of one or more of the proteins of the invention in recombinant host cells. In another aspect of the present invention, recombinant host cells are provided for the expression of PKS genes" (see Katz et al., page 2, column 2, paragraph 4; see also pages 8-27 showing specific examples; see especially, page 11, Table 1, Picromycin entry disclosing Applicants' elected narbomycin and pikromycin) (Please note that the reference for narbomycin by Xue et al. was incorporated by reference into Katz et al., see page 10, column 2, paragraph 2, "All of these publications are incorporated herein by reference ... The domains, modules and subunits that are described by the PKS genes listed in Table 1 as well as the genes for

polyketide modification or tailoring enzymes are among those that can be used in the practice of the present invention), which anticipates claims 2-9 and 17-19.

Response

18. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate" (e.g., see 2/2/2004 Response, pages 22, second to last paragraph).

[2] Applicants ague, "The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference" (e.g., see 2/2/2004 Response, page 22, second to last paragraph).

[3] Applicants argue that the 35 U.S.C. 102 rejection "undercuts" the 35 U.S.C. 112, first paragraph rejection (e.g., see 2/2/2004 Response, page 22, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully contends that Applicants' arguments are not clear. There are no "different biocatalyst functions" recited in the claims as purported by Applicants. There

are "different chemical functional groups", but not "different biocatalysts functions" (e.g., see claim 2). Thus, Applicants arguments are not commensurate in scope with the claimed invention.

[2] These statements are wholly unsubstantiated and thus without merit. Furthermore, the original rejection sets forth in great detail every element of the claimed invention and, as a result, contradict these assertions.

[3] Applicants' argument is not convincing since the above 35 U.S.C. 112, first paragraph rejections are "scope" rejections, which indicates, that a "portion" of Applicants' invention is indeed enabled by the specification, but points out that a much larger portion of the claimed invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 2**, the newly amended phrase "wherein said at least two biotransformation genes introduce two different chemical functional groups, at least one of the at least two different chemical functional groups for catalyzing processes for selected from the group selected from forming carbon to carbon bonds, hydroylation ..." is vague and indefinite because it is not clear whether Applicants intend the "two different functional groups" i.e., -OH, -C=C- to be "catalyzing processes for" carbon to carbon bond formation, hydroxylation etc or whether Applicants intend the enzymes that are produced by the transformed host cells to conduct such a process. Applicants are requested to clarify and/or correct. Therefore, claims 2 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
April 12, 2004

BENNETT CELSA
PRIMARY EXAMINER